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Thrombotic Thrombocytopenic Purpura

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Introduction

Background

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening multisystem disorder that is considered a true medical hematological emergency. Moschcowitz first described TTP in 1924 when he observed that a 16-year-old girl had anemia, petechiae, and microscopic hematuria. She died of multiorgan failure, and, at autopsy, disseminated microvascular hyaline platelet thrombi were prevalent in terminal arterioles and capillaries of the heart and kidneys. These platelet-rich thrombi remain the hallmark of the pathologic diagnosis. Microangiopathic hemolytic anemia along with the aggregation of platelet thrombi are present in a setting of microvascular injury and high fluid shear stress.

Varying degrees of organ ischemia due to the vascular occlusion occur. In this life-threatening disease, recognizing the clinical presentation and initiating medical intervention early are critical. This is difficult at times because there is a range of overlapping signs and symptoms with other microangiopathic diseases, such as hemolytic uremic syndrome (HUS). Both TTP and HUS have thrombocytopenia and microangiopathic hemolytic anemia but different medical management pathways. The patient may not present with all of the signs and symptoms of TTP, and there can be a gray zone as to which microangiopathy truly exists. TTP is a medical emergency with diagnostic criteria for treatment that is not always definitive but, if TTP is suspected, then the first-line treatment of plasma exchange should be initiated to save the patient's life.

Prior efforts to identify this disease clinically lead to the development of a diagnostic criteria classifying thrombotic thrombocytopenic purpura as a syndrome in 1966 by Amorosi and Ultmann. They reviewed 255 patients previously reported and 16 other patients. They outlined a pentad of clinical features including microangiopathic

hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction.[1] Later studies show this pentad is seen in 40% of cases. A triad of microangiopathic hemolytic anemia, thrombocytopenia, and neurologic abnormalities are seen in 74%.[2] Clinically, if a patient presents with thrombocytopenia (without coagulopathy), red cell fragmentation, elevated lactate dehydrogenase (LDH) level, and muscle and organ ischemia, consider TTP urgently in the differential diagnosis.[3]

Thrombotic microangiopathic diseases

Thrombotic thrombocytopenic purpura (TTP) is categorized into acquired (idiopathic) TTP and congenital (familial) TTP. Acquired TTP is mainly idiopathic, but there are other conditions and comorbidities besides idiopathic. Congenital TTP is a rare autosomal recessive disease present in childhood. Acquired and congenital TTP are both part of the larger spectrum of thrombotic microangiopathic diseases. These diseases have microvascular thrombosis and hemolysis with fragmented red blood cells.

TTP and hemolytic uremic syndrome (HUS) were once thought to have shared the pathophysiological etiology. Hemolytic uremic syndrome is usually found in children, and renal involvement is significant. Hemolytic uremic syndrome is caused by Shiga-like toxin-producing *E coli* O157:H7 in 90% of the cases.[4] Hemolytic uremic syndrome is characterized by a triad of hemolytic anemia, thrombocytopenia, and acute renal failure. TTP is usually found in adults and characterized by hemolytic anemia, thrombocytopenia, and, to a lesser extent, neurological manifestations. Symptoms are similar for TTP and HUS based solely on their clinical presentation. Microthrombi in TTP are mainly platelets, but microthrombi in HUS have more fibrin deposition.

Various terms have been used for other thrombotic microangiopathies such as TTP-like diseases, secondary TTP, or nonidiopathic TTP. In addition, TTP may also be drug-induced.[5] At times, distinguishing TTP from other thrombotic microangiopathies that have similar overlapping clinical presentations is very difficult. The complexity of categorizing these comorbidities or other conditions has not been resolved. Thrombotic microangiopathies have varying causes and pathology but present with clinical manifestations that are TTP-like. These include drugs such as quinine, ticlopidine, clopidogrel, and cyclosporine; cancers; vasculitis; hematopoietic stem cell transplantation; infections such as human immunodeficiency virus infection; and pregnancy, especially in the third trimester.[5] Further investigation is needed to classify this group.[6]

In 1977, a breakthrough in treatment was reported by Bukowski et al using whole-blood exchange transfusion, also known as plasmapheresis and fresh frozen plasma (FFP). Shortly after, Byrnes and colleagues used plasma infusion. During the plasma exchange, the entire plasma volume is replaced with normal human plasma and the large molecular inhibitory antibodies are removed and the plasma is replenished with the deficient protease. Delay in starting the plasma exchange is correlated with treatment failure. If a delay is unavoidable, begin plasma infusion until the plasma exchange is available. Intravenous (IV) plasma exchange is the present standard of treatment for thrombotic thrombocytopenic purpura. Fresh frozen plasma has become the standard replacement fluid with its plasma protein levels closely paralleling physiological levels.[3,7]

Plasma infusion and plasma exchange have had a significant impact on the life expectancy of patients. With the introduction of plasma exchange, the survival rate has improved from approximately 3% prior to the 1960s to 82%. By 1991, a landmark clinical trial by Rock et al presented evidence of the efficacy of plasma exchange treatment.[8] Early recognition of the clinical features and intervention with plasma exchange can reduce the mortality rate associated with TTP from 90% to approximately 10-20%. Early recognition and management are essential for patient survival. Plasma infusion is a temporary measure, and its use is limited by volume overload. Plasma exchange is the treatment of choice for patients with acquired TTP. Congenital TTP responds to plasma infusion.

Pathophysiology

The TTP syndrome is characterized by microangiopathic hemolysis and platelet aggregation/hyaline thrombi whose formation is unrelated to coagulation system activity. Platelet microthrombi predominate; they form in the microcirculation (ie, arterioles, capillaries) throughout the body causing partial occlusion of vessels. Organ ischemia, thrombocytopenia, and erythrocyte fragmentation (ie, schistocytes) occur. The thrombi partially occlude the vascular lumina with overlying proliferative endothelial cells. The endothelia of the kidneys, brain, heart, pancreas, spleen, and adrenal glands are particularly vulnerable to TTP. The liver, lungs, gastrointestinal tract, gallbladder, skeletal muscles, retina, pituitary gland, ovaries, uterus, and testes are also affected to a lesser extent. No inflammatory changes occur. The occlusion of the microthrombi affects many organs, and a myriad of symptoms are presented.

Mechanism

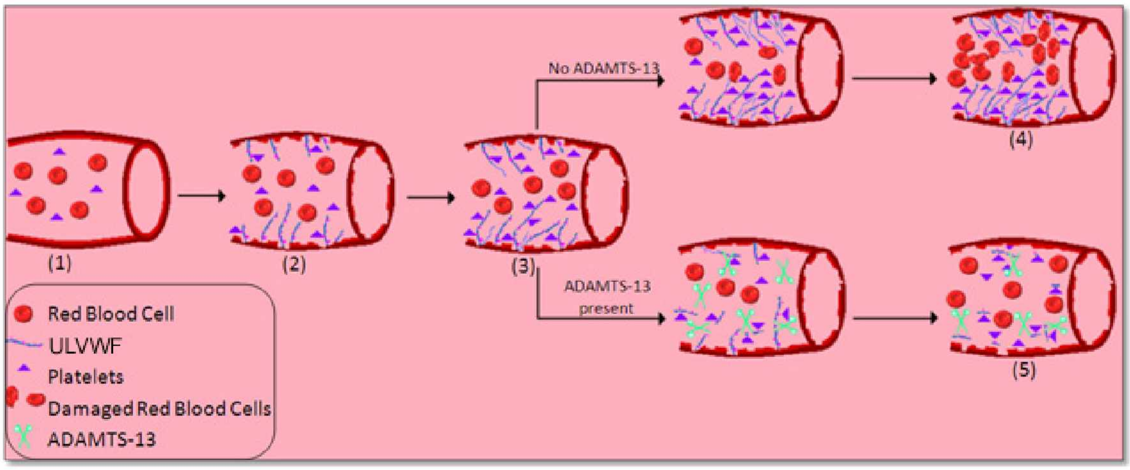
von Willebrand factor (vWF) was observed in 1982 by Moake and his colleagues. This is a large, adhesive glycoprotein that mediates thrombus formation at sites of vascular injury. vWF is synthesized in the endothelium and megakaryocytes, and it circulates in the plasma. Various sizes of multimers were noted, and the large form, ultralarge von Willebrand factor (ULVWF) multimers were secreted from the endothelium.[9] These are the largest soluble protein found in human plasma and are considered the major pathogenic factor in TTP due to the platelet clumping in the microvasculature.

The ULVWF is the most active of the various-sized multimers and is found in platelets, endothelial cells, and subendothelium. They were seen in the plasma of 4 patients with relapsing TTP.[10,11] The plasma of normal individuals has much smaller vWF. Moake suggested that there is a deficiency in an enzyme that reduces the large vWF to its normal size in plasma of patients with TTP. This large vWF appeared to have a greater ability to adhere with platelets mediating a thrombus formation. The large vWF combine with platelets consumed from the arterioles and capillaries of organs in a high-shearing stress environment and cause endothelial injury leading to ischemia. The red blood cells collide with the thrombi, and fragment leads to hemorrhage. As a result, the organ function is compromised.

The agitated endothelial cells are the main source of ULVWF multimer secretion into the bloodstream where they bind to specific surface platelet receptors. The ULVWF multimers adhere to the damaged endothelium or exposed subendothelium, with the platelet receptor binding to the ULVWF. The sheer stress of fluid and platelet thrombi

in the microcirculation does not enhance proteolysis of ULVWF but rather thrombi formation. How the ULVWF multimers-platelets thrombus is able to adhere and oppose the high velocity blood flow is unclear, and research is ongoing.[12]

In 1996, the von Willebrand factor-cleaving protease was isolated by two independent laboratories. Furlan, Lammle, and colleagues[13] in Switzerland and Tsai[14] in New York isolated the von Willebrand factor-cleaving protease known as ADAMTS-13. ADAMTS-13 is a metalloprotease consisting of multiple structural and functional domains and is the major regulator of the size of vWF in plasma. These domains may participate in the recognition and binding of ADAMTS-13 to vWF. The ULVWF multimers are cleaved by ADAMTS-13 as they are secreted from endothelial cells.



1) Sheer force of high velocity blood flow in microvasculature.
2) ULVWF is secreted from the endothelium adhering to damaged endothelium and subendothelium.
3) Platelets receptor binds to sites on the ULVWF.
4) ADAMTS13 is deficient therefore ULVWF are not cleaved, ULVWF-platelet thrombi increases and damaged RBC's increases.
5) ADAMTS13 cleaves the ULVWF to smaller VWF that are released to the circulation.

Thrombotic thrombocytopenic purpura. Image courtesy of Deepak Sharma.

Acquired TTP is associated with production of anti-ADAMTS13 antibodies inhibiting ADAMTS-13 activity. Congenital (familial) thrombotic thrombocytopenic purpura is associated with mutations of the vWF-cleaving protease ADAMTS-13 gene encoding, and ADAMTS-13 is inactivated or decreased. ADAMTS-13 is severely deficient in patients with both congenital TTP or acquired TTP. Furlan et al found in their investigation, including retrospective analysis of plasma samples, that an autoimmune mechanism may be responsible in patients with acquired deficiency of ADAMTS-13.[13]

Plasma exchange has been the first-line therapy for acquired TTP since 1991. Plasma infusion is used for congenital deficiency and can replace the deficiency and mutations in the ADAMTS-13 gene. Congenital TTP is a relapsing condition. For acquired TTP, more than 50% of patients with severe ADAMTS-13 deficiency relapse usually within

the year.[15] For acquired TTP, the inhibitor of ADAMTS-13 is removed by plasma exchange and is more effective than plasma infusion. Nevertheless, relapsing cases do occur in those with severe ADAMTS-13 deficiency.[11] The ULVWF is a marker found in the plasma of patients most likely to have a recurrence of TTP in acquired TTP, and this is also observed in congenital TTP.

ADAMST-13 multimers are abundant and fibrinogen/fibrin is minimal in TTP, whereas fibrinogen is abundant in disseminated intravascular coagulation (DIC). The life span of ADAMTS-13 is 2-4 days, and, if a relapse occurs after plasma exchange, then repeat treatment with plasma exchange is recommended. Certain immunosuppressive drugs and splenectomy are treatments for refractory cases of acquired TTP. Reasons for relapsing after plasma exchange in patients with severe ADAMTS-13 deficiency are unclear. An immune regulation defect may play a role in patients with recurrent ADAMTS-13 deficiency, but investigation is ongoing.

Future development in research

A greater focus on thrombotic thrombocytopenic purpura has emerged in recent years with advances in pathophysiology and diagnostic testing. Understanding the pathophysiology of thrombotic thrombocytopenic purpura is continuous and too early to have clearly defined evidence-based standards applicable to patient management and treatment.

Classification of thrombotic microangiopathies through better methods of assays measuring the ADAMTS-13 activity rather than the present-day cumbersome method of measuring the ADAMTS-13 proteolytic multimers, in addition to ways of detecting autoantibodies, and advances in our understanding of how ADAMTS-13 is regulated are forthcoming.[8]

Further research into replacement therapy with recombinant ADAMTS-13 instead of plasma[16] and reliable standardized assays with rapid results to measure ADAMTS-13 levels of activity will assist in diagnosis, leading to appropriate treatment plans. For example, differentiating TTP from HUS benefits the patient since plasma exchange is the treatment of choice for TTP not HUS, and plasma exchange is not a benign intervention. It is known that TTP has a severe deficiency in ADAMTS-13 not seen in HUS. Clinical trials using immunosuppressive treatments or alternative replacement fluids along with better prognostic measures for treatment are for the future.

vWF plays a role in occlusive arterial thrombosis and the possibility of ADAMTS-13 as a therapeutic instrument to discover ways of treating and managing more common platelet-mediated illnesses such as myocardial infarction and ischemic stroke is a beneficial research challenge.

Frequency

United States

More than 80 years ago, the occurrence rate of this uncommon disorder was 1 case per 1 million patients; however, the incidence rate is increasing, with the incidence rate a decade ago being 4-11 cases per 1 million patients. The incidence today is higher, with

greater awareness of this disorder and increasing reports of thrombotic thrombocytopenic purpura (TTP) in patients with comorbidities, conditions, and drug therapy.[17]

Incidence today is 6.5 cases per million per year, with a predominance in women. Less than 5% of cases are congenital.

Mortality/Morbidity

The mortality rate associated with thrombotic thrombocytopenic purpura (TTP) approached 100% until the 1980s; the drop in mortality rate since that time is attributed to earlier diagnosis and improvement in therapy with plasma exchange.

Presently, the mortality rate is approximately 95% for untreated cases. The survival rate is 80-90% with early diagnosis and treatment with plasma infusion and plasma exchange.

Thirty percent of patients who survive the initial episode experience one or more relapses within 2 years.

Race

No significant racial difference exists.

Sex

Thrombotic thrombocytopenic purpura is more common in women than in men, with a female-to-male ratio of 2:1 to 3:1.[18]

Age

Thrombotic thrombocytopenic purpura is most common in adults, although it can occur in neonates to persons as old as 90 years. The peak occurs in the fourth decade of life, with a median age at diagnosis of 35 years.

Clinical

History

- The pentad of findings associated with thrombotic thrombocytopenic purpura (TTP) is rarely found. Patients with TTP present with nonspecific complaints, and the current clinical factors leading to the diagnosis include the following:
    - Thrombocytopenia with petechial hemorrhages in the lower extremities and a lack of bleeding
    - Schistocytosis
    - Anemia - Hemoglobin levels less than 10 g/dL
    - Serum lactate dehydrogenase (LDH) levels often markedly elevated
    - Absence of other disease entities that could explain the thrombocytopenia and microcytic hemolytic anemia

- Neurologic changes
    - Altered mental status (36%) - Patients can present with confusion, generalized headaches, altered mental status, focal deficits, seizures, visual disturbances, and coma. Symptoms may wax and wane secondary to the microhemorrhagic and microocclusive vascular changes in the brain. CNS bleeding is an ominous sign.
    - Seizures (16%)
    - Hemiplegia (12%)
    - Paresthesias (4%)
- Renal changes (88%) with gross hematuria (15%)
- Fever (60%)
- Abdominal pain (24%) - May be related to gastrointestinal ischemia or pancreatitis[2]
- Cardiac changes
    - Heart failure
    - Arrhythmias
- Fatigue/generalized malaise
- Viral, flulike illness
- Arthralgias

Physical

Physical examination findings may be normal. Typical signs include the following:

- Fever
- Purpura - Nonpalpable small purpuric spots or petechiae occur with thrombocytopenia (ie, platelet count $<50 \times 10^9$/L)
- Petechial hemorrhages in the lower extremities
- Retinal hemorrhages
- Jaundice (ie, hemolysis)
- Severe hypertension (ie, renal failure)
- Neurologic deficits (eg, altered mental status, seizure)
- Splenomegaly

Causes

- Pregnancy can trigger congenital and acquired thrombotic thrombocytopenic purpura (TTP), especially second trimester and postpartum after delivery, and accounts for 10-25% of cases of TTP.[19]
    - TTP usually presents before 24 weeks' gestation and can be distinguished from other thrombotic microangiopathic disorders in that thrombocytopenia occurs without DIC.
    - Central nervous system (CNS) findings occur early and are disproportionate to alterations in blood pressure, renal dysfunction, or hepatic compromise.
    - The course of the syndrome is not altered by termination of pregnancy.
    - Improvement in survival rate is due to aggressive treatment with plasmapheresis or plasma transfusion.
- Cancers are associated with TTP, especially adenocarcinoma of the breast, gastrointestinal tract, and prostate cancer.[2]

- Anemia and thrombocytopenia occurring with TTP may be out of proportion to that expected from cancer and chemotherapy reactions.
  - LDH level is elevated, and the Coombs test result is negative.
  - In the cancer patient, coagulation factor consumption is often low.
  - Both TTP and DIC can be present in the same patient and may be difficult to distinguish.
  - TTP is associated with various infections.
- HIV-related TTP
  - Thrombotic microangiopathic disorder is uncommon but occurs in greater frequency in patients with HIV-1 infection; it may be the initial presentation.
  - The usual presentation is thrombocytopenia, MAHA, renal abnormalities, and neurologic dysfunction.
  - Serum LDH level is extremely elevated (ie, >1000 U/L); LDH level also is elevated with *Pneumocystis carinii* infection, high-grade B-cell lymphoma, and sulfa drug reactions.
- Autoimmune diseases such as systemic lupus erythematosus and other autoimmune diseases can present as idiopathic TTP with severe ADAMTS-13 deficiency and thrombotic microangiopathy.[20]
- Medication-induced TTP
  - Heparin is the most common medication associated with thrombocytopenia (3-7% of patients with IV heparin use).[22]
  - Ticlopidine and clopidogrel are closely related antiplatelet agents. TTP develops after 1-2 weeks of therapy. The mechanism causing TTP is not clear. ADAMTS-13 is identified in some but not all of the patients. Plasma exchange should be initiated early to reduce mortality from 60% to 14-20%.[20,21]
  - Quinine[2] an ingredient in some "tonic" water and an agent used for "night cramps of the legs" causes thrombocytopenia.[22]
  - Cancer chemotherapeutic agents associated with TTP include mitomycin C, tamoxifen, bleomycin, cytosine arabinoside, and daunomycin.
  - Noncancer chemotherapeutic and other drugs related to TTP include immunosuppressive agents (eg, cyclosporine A), crack cocaine, oral contraceptives, penicillin, and rifampin.
- Toxins (eg, bee venoms[23]) are associated with TTP.
- Autoimmune disorders
- Infectious process and sepsis
- Splenic sequestration
- Transplant-associated TTP
- Vasculitis
- Vascular surgery postoperative 5-9 days[2]
- Infections -*Streptococcus pneumonia*, cytomegalovirus[2]

Differential Diagnoses

Disseminated Intravascular Coagulation
Hemolytic Uremic Syndrome
Idiopathic Thrombocytopenic Purpura
Pregnancy, Eclampsia
Stroke, Hemorrhagic
Stroke, Ischemic

Other Problems to Be Considered

Autoimmune disorders
Cancer-associated TTP
Drug-induced TTP
HIV-related TTP
Infectious process and sepsis
Splenic sequestration
Transplant-associated TTP
Vasculitis

Workup

Laboratory Studies

Thrombotic thrombocytopenic purpura (TTP) is a clinical diagnosis with no pathognomonic laboratory test findings.

- Lactate dehydrogenase level is extremely elevated due, in part, to ischemic or necrotic tissue cells rather than to hemolysis.
- Platelets less than 20,000/µ L
- Plasma haptoglobin – Decreased
- Complete blood count (CBC)
  - Hemoglobin less than 10 g/dL
  - Thrombocytopenia - Evidence of thrombocytopenia may precede the appearance of fragmented RBCs and LDH elevation by several days.
- Peripheral blood smear - Fragmented RBCs (ie, schistocytes) are consistent with hemolysis. Schistocytes on a blood smear is the morphologic hallmark of the disease, but no guidelines exist as to the number of schistocytes required to differentiate TTP from other thrombotic microangiopathies.
- LDH level - Indirect bilirubin level - Elevated
- Direct bilirubin – Normal
- Reticulocyte count - Elevated
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) - Normal
- DIC panel (eg, fibrinogen, D-dimer) - The results are usually normal. Increasing D-dimer levels are the most specific DIC parameter and reflect fibrinolysis of cross-linked fibrin.
- Pregnancy test - This helps to identify the 10-25% of patients with TTP who are pregnant or postpartum.
- Creatinine level - Mildly elevated (46%)

- HIV testing - This test helps to identify patients with HIV in whom TTP is the presenting symptom.
- Urinalysis - Proteinuria and microscopic hematuria
- ADAMTS-13 activity assay is used to measure the activity level of the ADAMTS-13 protease. Measuring ADAMTS-13 activity or ADAMTS antigen levels via ELISA assay as a single test to distinguish TTP from HUS is not practical at this time. The absence of in vitro tests capable of detecting abnormalities in all the molecular interactions required for the cleavage of ULVWF multimers by ADAMTS-13 in vivo is a limitation.

Imaging Studies

CT scan of the head may be indicated to assess for intracranial bleeding and infarcts.

Other Tests

Bone marrow or gingival biopsy samples yield diagnostic lesions (hyaline thrombi) in 30-50% of cases. This is not a necessary test for diagnosis of TTP.

Treatment

Emergency Department Care

Practice diagnostic criteria for initiating therapy are thrombocytopenia, schistocytosis, and significant elevations in serum LDH levels.

- Thrombocytopenia - Platelets
- Schistocytosis - Peripheral smear
- Elevated serum LDH levels
- Look for other disease entities that could explain the thrombocytopenia and microcytic hemolytic anemia such as disseminated intravascular coagulation (DIC).
- Once thrombotic thrombocytopenic purpura (TTP) is included in the differential diagnosis and other causes are eliminated, contact a hematologist. As a team, the patient is managed with plasma exchange, antiplatelet agents (eg, dipyridamole, aspirin, steroids), and supportive care for the various complaints. Splenectomy for refractory cases is not an emergency medicine issue. Survival rate and prognosis are poor, and, in most instances, the chance for survival is time-specific.

Plasma exchange

Use a device with a wide-bore, 2-lumen catheter at the femoral site. Use blood-cell separators so that the patient's plasma is removed and replaced by standard replacement fluid, fresh frozen plasma (FFP), to eliminate ADAMTS-13 autoantibodies. Start with a single plasma volume and exchange FFP at a rate of 40 mL/kg of body mass. A plasma exchange twice a day may be necessary for resolution of thrombocytopenia and neurologic complications if the response to the initial daily exchange is poor. The procedure may be repeated for days to weeks for effect. The target platelet level is

150,000/µ L, although this number is variable. A declining lactate dehydrogenase level indicates a positive response to treatment. Complications include death, systemic infections, allergic reaction, catheter or venous thrombosis, serum sickness, fever, and hypocalcemia from citrate.[2]

Infusion of high-dose FFP (30 mL/kg) is used as a temporizing measure until the patient can be transferred to a facility where plasma exchange is available. Patients with congenital TTP undergo infusion therapy using 10-15 mL of FFP per kg of body weight every 2-3 weeks.[24]

Other treatments

Cryosupernatant is the residual plasma fraction after the separation of cryoprecipitate that can be used in plasma exchange, but it has not been found to be better than FFP.

Antiplatelet agents aspirin and dipyridamole have been used since the 1970s, but their use is controversial. Hemorrhage is a concern, and these agents' benefit has not been proven. Other antiplatelet agents (eg, ticlopidine, prostacyclin) have variable outcomes.

Platelet-depleted packed RBCs may be necessary for severe hemolytic anemia.

Splenectomy sequesters red blood cells, platelets, and B cells that produce antibodies to VWF-cleaving protease.[2] Splenectomy is performed occasionally to treat patients who do not respond to plasma exchange or who relapse chronically. Some patients benefit from splenectomy and others do not. The spleen is a major site of microvascular occlusive lesions in severe TTP.

Hemodialysis as supportive care for end-organ damage may be required.

Medications including angiotensin-converting enzyme (ACE) inhibitors, nitroprusside, or esmolol may be required to control severe hypertension. Anticonvulsants, such as phenytoin, may be required to control seizures.

Contraindications

Platelet transfusion is contraindicated because it is associated with rapid deterioration. The platelet aggregation worsens with platelet transfusions. In some studies, extensive platelet aggregates were found throughout the CNS on postmortem examination.

Heparin and fibrinolytic agents are contraindicated due to their increase bleeding risk and ineffectiveness.[2]

Desmopressin (DDAVP) is contraindicated because it acts by releasing ULVWF from the endothelium into the circulating blood.

Consultations

Early consultation with a hematologist is beneficial because of the diagnostic and management complexity of TTP.

The differential diagnosis is extensive for thrombocytopenia, but early recognition of TTP is essential for the patient's survival.

Medication

The goal of therapy is to reduce destruction of platelets.

Glucocorticoids

These agents have immunosuppressant activity.

Prednisone (Sterapred)

Glucocorticoids inhibit phagocytosis of antibody-covered platelets. Treatment of hemolytic anemia during pregnancy is conservative unless disease is severe (use lowest dose of glucocorticoids). In neonates, if platelet count drops below 50-75 X 10^9/L, consider prednisone and exchange transfusions of immune globulin.

Dosing

Adult

1-2 mg/kg/d PO divided bid/qid; until remission occurs

Pediatric

4-5 mg/m^2/d PO; alternatively, 1-2 mg/kg PO divided bid/qid; taper over 2 wk as symptoms resolve

Interactions

Estrogens may decrease clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics

Contraindications

Documented hypersensitivity; viral, fungal, connective tissue, or tubercular skin infections; peptic ulcer disease; hepatic dysfunction; GI disease

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur

Immunosuppressant agents

These agents inhibit key factors involved in immune reactions. In addition to the drugs listed below, treatment of refractory or relapsing TTP includes vincristine, a second-line therapy with an unknown mechanism of action. Vincristine is occasionally given to treat resistant cases, but it has no proven benefit. Dosing is 1 mg/m^2, with a maximum dose of 2 mg, given weekly.

Rituximab (Rituxan)

Indicated to reduce signs and symptoms for moderately-to-severely active rheumatoid arthritis in combination with methotrexate. For use in adults who have experienced an inadequate response to one or more TNF antagonist therapies. Antibody genetically engineered. Chimeric murine/human monoclonal antibody directed against the CD20 antigen found on surface of B lymphocytes.

Dosing

Adult

1000 mg IV infusion for 2 doses, separated by 2 wk; administer methylprednisolone 100 mg IV (or its equivalent) 30 min before each infusion to reduce infusion related reactions
Do not exceed infusion rate of 50 mg/h initially; if hypersensitivity or infusion-related reactions do not occur, may escalate infusion rate by 50 mg/h increments q30min; not to exceed 400 mg/h

Pediatric

Not established

Interactions

Coadministration with cisplatin is known to cause severe renal toxicity including acute renal failure; may interfere with immune response to live virus vaccine (MMR) and reduce efficacy (do not administer within 3 mo of vaccine)

Contraindications

Documented hypersensitivity; IgE-mediated reaction to murine proteins

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Use with caution in patients with dormant infections such as hepatitis B, hepatitis C, or CMV due to risk of reactivation; hypotension, bronchospasm, and angioedema may occur, premedication with acetaminophen and diphenhydramine may decrease incidence; discontinue treatment if life-threatening cardiac arrhythmias occur; must administer by slow IV infusion, do not administer IV push or bolus

Cyclophosphamide (Cytoxan, Neosar)

Cyclic polypeptide that suppresses some humoral activity. Chemically related to nitrogen mustards. Activated in the liver to its active metabolite, 4-hydroxycyclophosphamide, which alkylates the target sites in susceptible cells in an all-or-none type reaction. As an alkylating agent, the mechanism of action of the active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells.
Biotransformed by cytochrome P-450 system to hydroxylated intermediates that break down to active phosphoramide mustard and acrolein. Interaction of phosphoramide mustard with DNA considered cytotoxic.
When used in autoimmune diseases, mechanism of action is thought to involve immunosuppression due to destruction of immune cells via DNA cross-linking.
In high doses, affects B cells by inhibiting clonal expansion and suppression of production of immunoglobulins. With long-term low-dose therapy, affects T-cell functions.

Dosing

Adult

500-750 mg/m^2 IV qmo

Pediatric

Administer as in adults

Interactions

Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of quinolones; toxicity may increase with chloramphenicol; may increase effect of anticoagulants; coadministration with high

doses of phenobarbital may increase leukopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leukopenia; coadministration with succinylcholine may increase neuromuscular blockade by inhibiting cholinesterase activity

Contraindications

Documented hypersensitivity; severely depressed bone marrow function

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; regularly examine urine for RBCs, which may precede hemorrhagic cystitis

Cyclosporine (Neoral, Sandimmune)

An 11-amino acid cyclic peptide and natural product of fungi. Acts on T-cell replication and activity.
Specific modulator of T-cell function and an agent that depresses cell-mediated immune responses by inhibiting helper T-cell function. Preferential and reversible inhibition of T lymphocytes in G0 or G1 phase of cell cycle suggested.
Binds to cyclophilin, an intracellular protein, which, in turn, prevents formation of interleukin 2 and the subsequent recruitment of activated T cells.
Has about 30% bioavailability, but there is marked interindividual variability.
Specifically inhibits T-lymphocyte function with minimal activity against B cells.
Maximum suppression of T-lymphocyte proliferation requires that drug be present during first 24 h of antigenic exposure.
Suppresses some humoral immunity and, to a greater extent, cell-mediated immune reactions (eg, delayed hypersensitivity, allograft rejection, experimental allergic encephalomyelitis, and graft-vs-host disease) for a variety of organs.

Dosing

Adult

Clinical and immunological effects correlate with serum concentration, and dose usually adjusted to achieve trough serum level of 100-200 ng/mL (as determined by HPLC)
4-10 mg/kg/d PO in 2-3 divided doses has been used

Pediatric

Administer as in adults

Interactions

Carbamazepine, phenytoin, isoniazid, rifampin, and phenobarbital may decrease cyclosporine concentrations; azithromycin, itraconazole, nicardipine, ketoconazole, fluconazole, erythromycin, verapamil, grapefruit juice, diltiazem, aminoglycosides, acyclovir, amphotericin B, and clarithromycin may increase cyclosporine toxicity; acute renal failure, rhabdomyolysis, myositis, and myalgias increase when taken concurrently with lovastatin; methylprednisolone and cyclosporine mutually inhibit one another resulting in increased plasma levels of each drug

Contraindications

Documented hypersensitivity; uncontrolled hypertension or malignancies; do not administer concomitantly with PUVA or UVB radiation in psoriasis since it may increase risk of cancer

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Evaluate renal and liver functions often by measuring BUN, serum creatinine, serum bilirubin, and liver enzymes; may increase risk of infection and lymphoma; reserve IV use only for those who cannot take PO

Follow-up

Further Inpatient Care

Emergency medicine is acute care management to stabilize the patient with thrombotic thrombocytopenic purpura (TTP) for continued care. Follow-up is referred to internal medicine.

Miscellaneous

Medicolegal Pitfalls

Thrombotic thrombocytopenic purpura (TTP) is a hematologic emergency. It is a multisystem disease that can cause rapid deterioration of the patient's neurologic, renal, and hematologic status. TTP is an uncommon disease with a high fatality rate if untreated or misdiagnosed. Rapid diagnosis and aggressive treatment by therapeutic plasma exchange are necessary to reduce the risk of a fatal outcome.

TTP is difficult to diagnose because the patient's presentation can be nonspecific and the characteristic pentad of symptoms may not occur together. Other disease entities can

have some of the same symptoms.

To avoid the devastating pitfall of misdiagnosing a patient include TTP in the differential diagnosis of diseases in a patient with new-onset thrombocytopenia, schistocytosis, and marked elevation of LDH value. Treatment with platelet infusion can be fatal in patients with TTP but beneficial in DIC; therefore, including TTP in the differential diagnosis is critical.

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Keywords

thrombocytopenic purpura, Moschcowitz disease, thrombotic thrombocytopenic purpura, TTP, multisystem disorder, plasma exchange, fresh-frozen plasma, FFP, microangiopathic hemolytic anemia, hemolytic uremic syndrome, HUS, familial thrombotic thrombocytopenic purpura, familial TTP, acquired idiopathic thrombotic thrombocytopenic purpura, acquired idiopathic TTP, von Willebrand factor multimers, vWF, vWF multimers, vWF-cleaving protease, anemia, petechiae, microscopic hematuria, disseminated microvascular thrombi, thrombocytopenia, renal dysfunction, Escherichia coli, E coli O157:H7, Shigalike toxin, microangiopathic hemolysis, platelet microthrombi, ultralarge von Willebrand factor multimers, ULVWF multimers, ADAMTS-13 gene mutations, ULVWF multimer–induced platelet thrombosis, ULVWF-cleaving protease, petechial hemorrhages, seizures, CNS bleeding, heart failure, arrhythmias, gross hematuria, purpuric spots, plasmapheresis, plasma transfusion, thrombotic microangiopathic

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